CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

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The chemicals listed in the table below may meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism as known to the State to cause cancer. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

U.S. Environmental Protection Agency (U.S. EPA) is one of five institutions which have been identified as authoritative bodies for identification of chemicals as causing cancer for the purposes of Proposition 65 (Title 22, Cal. Code of Regs., section 12306(1)). U.S. EPA has identified each of the chemicals in the table below as causing cancer. The Office of Environmental Health Hazard Assessment (OEHHA) has found that these chemicals appear to be "formally identified" as causing cancer according to the regulations covering this issue (Title 22, Cal. Code of Regs., section 12306(d)). The chemicals below are the subjects of reports published by the authoritative bodies that conclude that the chemicals cause cancer. Also, the documents specifically and accurately identify the chemicals, and the documents meet one or more of the criteria outlined in Title 22, Cal. Code of Regs., section 12306(d)(2).

OEHHA also finds that the criteria given in regulation for "as causing cancer" (Title 22, Cal. Code of Regs., section 12306(e)) appear to have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative body in making their findings that the specified chemicals cause cancer. A brief discussion of the relevant carcinogenesis studies providing evidence for the findings is presented below. The statements in bold reflect data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for carcinogenicity (Title 22, Cal. Code of Regs., section 12306(e)). The full citations for the authoritative body documents are given in this report.

Chemicals Under Consideration for Possible Listing as Known to the State to Cause Cancer

Chemical	CAS No.	Chemical Use	Reference
Iprovalicarb	140923-17-7; 140923-25-7	Fungicide used on imported grapes and raisins. Not registered by U.S. EPA.	U.S. EPA (2002)
Nitrapyrin	1929-82-4	Nitrogen stabilizer for ammonia and urea nitrogen fertilizers.	U.S. EPA (2000)
Propoxur	114-26-1	Used for the control of various insects such as earwigs, cockroaches, spiders, ants, silverfish and clover mites.	U.S. EPA (1996)

Iprovalicarb (CAS No. 140923-17-7 ;CAS No. 140923-25-7)

Increased incidence of malignant tumors in male and female rats, to an unusual degree with respect to site, and at multiple rare sites in female rats.

U.S. EPA (2002) has concluded that iprovalicarb is "likely to be a human carcinogen" based on the occurrence of rare tumors in male and female rats. The studies considered by U.S. EPA (2002) are briefly described below.

Male and female Wistar rats (50 rats/group/sex) were exposed to iprovalicarb via diet for 24 months. An additional 10 rats/group/sex were exposed to iprovalicarb and sacrificed at 12 months. Two male rats developed osteosarcoma of the femur and one developed osteosarcoma of the lower jaw. The combined incidence of osteosarcomas (0/50, 0/50, 0/49, 3/50 [$p<0.05$]; $p<0.01$ for dose related trend) was significantly greater than that in control animals. In addition, one chondrosarcoma of the nasal cavity was observed in an animal receiving the highest dose of iprovalicarb. U.S. EPA (2002) considered chondrosarcoma and osteosarcoma as having a common etiology but could not combine these tumors for statistical analyses since the nasal cavity of only the one rat with a gross nasal lesion was examined microscopically. Both chondrosarcomas and osteosarcomas are rare malignant tumors. In the historical control data for three substrains of Wistar rats from the performing laboratory, no osteosarcomas or chondrosarcomas were reported in 698 male and 700 female control rats in 14 two-year studies. In additional historical control data submitted by the testing laboratory, one osteosarcoma was found in a control male rat (total number of rats not indicated).

U.S. EPA (2002) concluded that there were also rare tumors at multiple sites in female rats. These included malignant mixed Mullerian tumors of the uterus (0/49, 0/49, 1/48, and 2/48 for control, low-, mid- and high dose groups, respectively) and benign transitional cell papillomas of the urinary bladder (0/49, 0/48, 0/48 and 2/48). Two malignant squamous cell carcinomas of the clitoral gland were observed in two high dose

animals; these two were the only animals examined microscopically for tumors of the clitoral gland. In addition to the above tumors, thyroid follicular cell adenomas (0/49, 0/49, 1/48 and 2/48) and carcinomas (0/49, 0/49, 1/48 and 1/48) were observed. The combined incidence of thyroid follicular cell adenoma or carcinoma (0/49, 0/49, 2/48 and 3/48) occurred with a statistically significant trend ($p<0.05$). Thyroid follicular cell tumors are considered uncommon tumors in female Wistar rats (U.S. EPA, 2002). No treatment related tumors were observed in studies with male or female $B6C3F_1$ mice.

Nitrapyrin (CAS No. 1929-82-4)

Increased incidence of malignant and combined malignant and benign tumors in male and female mice with tumors at multiple and uncommon sites.

U.S. EPA (2000) has concluded that nitrapyrin [2-chloro-6-(trichloromethyl) pyridine] is "likely to be carcinogenic in humans." The U.S. EPA (2000) evaluation was the second review of nitrapyrin. The chemical was first evaluated in 1992 at which time U.S. EPA (1992) concluded that renal tubular adenomas and adenocarcinomas observed in male rats were associated with α_{2u}-globulin-induced nephropathy and that a mouse study was inadequate for carcinogenicity assessment. Nitrapyrin was classified in Group D, not classifiable as to human carcinogenicity. In 2000, nitrapyrin was re-evaluated to assess newly completed mouse carcinogenicity studies. These studies are briefly described below.

Male and female $B6C3F_1$ mice (50/group/sex) received nitrapyrin via diet for two years. Multiple tumors developed in both male and female mice. In male mice, tumors of the liver, stomach and epididymis were increased. There were statistically significant increases in the incidences of hepatocellular adenomas (12/49, 19/50 and 45/48 [$p< 0.01$] for control, low- and high-dose animals, respectively) and combined hepatocellular adenomas or carcinomas (17/49, 20/50, 46/49 [$p< 0.01$]). The incidence of hepatocellular carcinomas (7/49, 3/50, 12/49) was also increased, but did not reach statistical significance. Increases in squamous cell tumors of the nonglandular stomach (papillomas: 1/43, 9/49 and 12/36 [$p<0.01$]; carcinomas: 0/43, 0/49 and 3/38 [$p<0.01$]; combined papillomas and carcinomas: 1/43, 9/49 and 15/38 [$p<0.01$]) were statistically significant. U.S. EPA (2000) noted that these are rare tumors. A statistically significant increase in testicular undifferentiated epididymal sarcomas (0/40, 2/48 and 4/33 [$p< 0.05$]) was also observed in high-dose male rats. U.S. EPA (2000) noted the finding in the high dose group was significant and also considered the increase in sarcomas at the low dose (2/48) to be biologically significant and noted that these were also rare tumors.

Nitrapyrin-treated female mice developed tumors of the stomach, liver, and Harderian gland. Incidences of stomach nonglandular squamous cell papillomas (1/47, 8/48 [$p<0.05$] and 21/48 [$p<0.01$] for control, low- and high-dose animals, respectively) and combined squamous cell papillomas or carcinomas of the nonglandular stomach (1/47,

8/48 [p<0.05], 22/48 [p<0.01]) were also significantly increased. The incidence of squamous cell carcinoma of the nonglandular stomach (0/47, 0/48, 2/48) was not statistically significant, but U.S. EPA (2000) considered the increase in carcinomas at the high dose (2/48) to be biologically significant. The incidences of these tumors were outside the historical control range (historical range for papillomas of the nonglandular stomach: 0-1%; for carcinomas: 0%). There were also statistically significant increases in the incidences of hepatocellular adenomas and combined adenomas and carcinomas in treated mice. The incidence of hepatocellular adenoma was 6/47, 27/48 [p<0.01] and 32/48 [p<0.01] for control, low- and high-dose groups, respectively. The combined incidence of adenomas or carcinomas was 6/47, 38/48 [p<0.01] and 33/48 [p<0.01]. The incidence of hepatocellular carcinoma (0/47, 1/48 and 2/48) was also increased although not significantly. In addition, statistically significant increases in Harderian gland adenomas (1/47, 8/48 and 9/48 [p<0.01]) were observed.

Propoxur (CAS No. 114-26-1)

Increased incidence of malignant and combined malignant and benign tumors in male and female rats.

U.S. EPA (1996) has concluded that propoxur is a probable human carcinogen (Group B2). The 1996 evaluation was the fourth U.S. EPA evaluation of propoxur. Propoxur was first classified in Group B2 in 1986 and was re-evaluated in 1990 and again in 1991. In all evaluations, U.S. EPA concluded that propoxur should be classified as a probable human carcinogen. Relevant studies are briefly summarized below.

In studies conducted in 1984, male and female Wistar rats (50 animals/group/sex) were exposed to propoxur via diet for two years. Statistically significant increases in the incidence of papillomas and carcinomas of the urinary bladder were observed in both male and female rats. In male rats, the incidence of bladder carcinomas (0/48, 0/50, 0/49 and 8/49 for control, low-, mid- and high-dose groups, respectively) was significantly greater in the high dose group compared to that in control animals [p<0.01]. The combined incidence of bladder papillomas and carcinomas (0/48, 0/50, 1/49 and 33/49) was also significantly greater in the high dose group compared to that in control animals [p<0.01]. In female rats, the incidence of bladder carcinomas (0/47, 0/46, 0/47 and 5/48) was significantly greater in the high-dose group than in the control group [p<0.05]. The combined incidence of bladder carcinomas and papillomas in female rats was 0/47, 0/46, 0/47, and 33/48 [p<0.01]. There was also a significant dose-related trend [p=0.024] associated with the incidence of carcinoma of the uterus (3/48, 4/48, 3/47, and 8/47). U.S. EPA reported in its 1986 evaluation that this increase was associated with early dose-related deaths and that there was an earlier onset of uterine carcinoma in the high dose group (U.S. EPA, 1996).

In a 1988 study, female Wistar rats (70 animals/group) were exposed to propoxur via diet for up to two years. During the two-year period, a considerable number of animals (40 or more/group) were sacrificed. For animals that died between 78 weeks and the final two-year sacrifice or were sacrificed at two years, the combined incidence of urinary bladder papilloma or carcinoma was 0/29, 0/24, 0/29, 0/26, 6/29 [p=0.0117], 13/29 [p<0.001], and 10/24 [p<0.001](for control, 50, 250, 1000, 3000, 5000 and 8000 ppm groups, respectively). Uterine carcinomas were reported in two female rats in the highest dose group. Upon re-evaluation, the incidence was found to be 1/17, with the second tumor reclassified as a carcinoma *in situ*.

In studies conducted in 1992, male and female B6C3F_1 mice (50 animals/group/sex) were exposed to propoxur via diet for two years. In male mice, the incidence of hepatocellular adenoma (10/49, 10/49, 15/49 and 21/50, for control, low-, mid- and high-dose animals, respectively) was significantly greater in the high-dose group than in the control group [p<0.05]. The combined incidence of hepatocellular adenoma and carcinoma in male mice was 15/49, 16/49, 23/49, and 26/50 [p<0.05].

REFERENCES

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